Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Cancelled).

2. (Previously Presented) The method of claim 6, wherein the marker that reflects the activity of osteoblasts is:

(1) a marker associated with the phase of osteoblasts proliferation and matrix formation and a marker associated with the phase of calcification; or

(2) a marker associated with the phase of matrix maturation and a marker associated with the phase of calcification.

3. (Previously Presented) The method according to claim 6, wherein the marker that reflects the activity of osteoblasts is:

1) Carboxyterminal propeptide of type I procollagen or Amino terminal propeptide of type I procollagen and osteocalcin; or

2) Bone specific alkaliphosphatase and osteocalcin.

4. (Previously Presented) The method according to claim 6, wherein the marker that reflects the activity of osteoclasts is a marker associated with bone type I collagen.

5. (Previously Presented) The method according to claim 6, wherein the marker that reflects the activity of osteoclasts is deoxypyridinoline and/or Carboxyterminal telopeptide of type I collagen.

6. (Previously Presented) A method of diagnosing amelioration and/or exacerbation of metastasis of malignant tumor to bone in a patient with a cancer disease,

using markers for bone formation that reflect the activity of osteoblasts and markers that reflect the activity of osteoclasts,

1) wherein the markers that reflect the activity of osteoblasts are

a) a marker associated with the phase of calcification, and

b) a marker associated with the phase of osteoblasts proliferation and/or matrix formation,

2) wherein the marker that reflects the activity of osteoclasts is a marker associated with osteoclasts targeted to evaluation of worsening of the disease,

whereby the amelioration of bone metastasis or therapeutic effect and the degree of the exacerbation of bone metastasis are diagnosed correctly by monitoring said two markers, one associated with osteoblasts and targeted to evaluation of therapeutic effect, and the other associated with osteoclasts and targeted to evaluation of worsening of the disease.

7. (Cancelled).

8. (Previously Presented) In a method of evaluating the efficacy of drugs for treatment of a cancer disease,

using a formative marker that reflects the activity of osteoblasts or a marker that reflects the activity of osteoclasts,

1) wherein the markers that reflect the activity of osteoblasts are

a) a marker associated with the phase of calcification, and

b) a marker associated with the phase of osteoblasts proliferation and/or matrix formation,

2) wherein the marker that reflects the activity of osteoclasts is a marker associated with osteoclasts targeted to evaluation of worsening of the disease,

whereby the amelioration of bone metastasis or therapeutic effect and the degree of the exacerbation of bone metastasis are diagnosed correctly by monitoring said two markers, one associated with osteoblasts and targeted to evaluation of therapeutic effect, and the other associated with osteoclasts and targeted to evaluation of worsening of the disease.

9. (Previously Presented) The method according to claim 8, wherein the drug evaluated is a cancer control therapeutic agent.

10. (Previously Presented) The method according to claim 8, wherein the drug evaluated is a bone resorption suppressant.

11. (Previously Presented) The method according to claim 8, wherein the drug evaluated is an endocrine therapeutic agent.

12. (Previously Presented) The method according to claim 8, wherein the marker that reflects the activity of osteoblasts is:

(1) a marker associated with the phase of osteoblast proliferation and matrix formation and a marker associated with the phase of calcification; or

(2) a marker associated with the phase of matrix maturation and a marker associated with the phase of calcification.

13. (Previously Presented) The method according to claim 8, wherein the marker that reflects the activity of osteoblasts is:

(1) Carboxyterminal propeptide of type I procollagen or Amino terminal propeptide of type I procollagen and osteocalcin; or

(2) Bone specific alkaliphosphatase and osteocalcin.

14. (Previously Presented) The method according to claim 8, wherein the marker that reflects the activity of osteoclasts is a marker associated with bone type I collagen.

15. (Previously Presented) The method according to claim 8, wherein the marker that reflects the activity of osteoclasts is deoxypyridinoline and/or Carboxyterminal telopeptide of type I collagen.

16-24 (Cancelled).

25. (Previously Presented) The method according to claim 6 or 8, wherein said cancer disease is prostate cancer.

26. (Previously Presented) The method according to claim 6 or 8, wherein said cancer disease is breast cancer.

27. (Previously Presented) The method according to claim 8, wherein the drug evaluated is a cancer control therapeutic agent.

28. (Previously Presented) The method according to claim 8, wherein the drug evaluated is a bone resorption suppressant.

29. (Previously Presented) The method according to claim 8, wherein the drug evaluated is an endocrine therapeutic agent.

30. (Previously Presented) A method of evaluating the efficacy of a drug for the treatment of cancer or for the inhibition or amelioration of a metastasis of said cancer to bone in a patient with cancer, wherein said cancer is selected from the group consisting of prostate cancer and breast cancer,

which comprises measuring for both (1) osteocalcin and (2) one marker selected from the group consisting of BALP, PICP and PINP,

determining a Z value for each of said osteocalcin and said BALP, PICP or PINP, each said Z value being determined by dividing the difference between said measured value for said patient and an average value for patients without bone metastasis, by a standard deviation of a patient without bone metastasis, and determining a crossover index by dividing said Z value for osteocalcin by said Z value for BALP, PICP or PINP,

said crossover index providing a diagnosis of progression of bone metastasis and evaluation of drug efficacy in the treatment of said patient for said cancer;

wherein assessing or judging amelioration and/or exacerbation of metastasis with regard to the Z value is carried out in comparison with data for CR, PD, IMP and/or NC.

31 and 32 (Cancelled).

33. (Previously Presented) A method of diagnosing amelioration and/or exacerbation of metastasis of malignant tumor to bone in a patient with breast cancer,

using markers that reflect the activity of osteoblasts and markers that reflect the activity of osteoclasts,

1) wherein the markers that reflect the activity of osteoblasts are

(a) a marker associated with the phase of calcification, and

(b) a marker associated with the phase of osteoblasts proliferation and/or matrix formation,

2) wherein the marker that reflects the activity of osteoclasts is a marker associated with osteoclasts targeted to evaluation of worsening of the disease,

comprising testing blood from said patient for a marker of bone metabolism,

wherein the amelioration of bone metastasis or therapeutic effect and the degree of the exacerbation of bone metastasis are diagnosed by monitoring said markers, and

said testing comprising measuring for both osteocalcin and BALP,

determining a Z value for each of said BALP and osteocalcin, each said Z value being determined by dividing the difference between said measured value for said patient and an average value for patients without bone metastasis, by a standard deviation of a patient without bone metastasis, and

determining a crossover index by dividing said Z value for osteocalcin by said Z value for BALP,

said crossover index providing a diagnosis of progression of bone metastasis in the treatment of said patient for breast cancer.

34. (Previously Presented) A method of evaluating the efficacy of drugs for treatment of breast cancer,

using a formative marker that reflects the activity of osteoblasts and a marker that reflects the activity of osteoclasts,

1) wherein the markers that reflect the activity of osteoblasts are

(a) a marker associated with the phase of calcification, and

(b) a marker associated with the phase of osteoblasts proliferation and/or matrix formation,

2) wherein the marker that reflects the activity of osteoclasts is a marker associated with osteoclasts targeted to evaluation of worsening of the disease,

comprising testing blood from said patient for a marker of bone metabolism,

wherein the amelioration of bone metastasis or therapeutic effect and the degree of the exacerbation of bone

metastasis are diagnosed correctly by monitoring said markers, and

said testing comprises measuring for both osteocalcin and BALP,

determining a Z value for each of said osteocalcin and said BALP, each said Z value being determined by dividing the difference between said measured value for said patient and an average value for patients without bone metastasis, by a standard deviation of a patient without bone metastasis, and

determining a crossover index by dividing said Z value for osteocalcin by said Z value for BALP,

said crossover index providing a diagnosis of progression of bone metastasis and evaluation of drug efficacy in the treatment of said patient for said cancer; wherein a higher index indicates amelioration of the patient's condition.

35- 36 (Cancelled).